STUDY OF EXTRA INTESTINAL MANIFESTATIONS OF INFLAMMATORY BOWEL DISEASE

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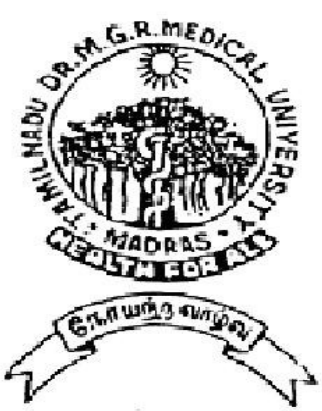

The Tamilnadu Dr.M.G.R.Medical University
Chennai – 600 032.

MADURAI MEDICAL COLLEGE, MADURAI.

CERTIFICATE

This is to certify that this dissertation titled "**STUDY OF EXTRA INTESTINAL MANIFESTATIONS OF INFLAMMATORY BOWEL DISEASE"** submitted by **DR. JEFFEY GEORGE** to the faculty of General Medicine, **The Tamil Nadu Dr. M.G.R. Medical University, Chennai** in partial fulfillment of the requirement for the award of MD degree branch I General Medicine, is a bonafide research work carried out by him under our direct supervision and guidance.

DR.V.T.PREM KUMAR, M.D
Professor of Medicine,
Chief, VI Medical Unit,
Madurai Medical College,
Madurai.

DR. A. AYYAPPAN, M.D,
Professor & HOD,
Department of Medicine,
Madurai Medical College,
Madurai.

DECLARATION

I, **Dr. JEFFEY GEORGE,** solemnly declare that the dissertation titled **"STUDY OF EXTRA INTESTINAL MANIFESTATIONS OF INFLAMMATORY BOWEL DISEASE "** has been prepared by me.

This is submitted to **The Tamil Nadu Dr. M.G.R. Medical University, Chennai,** in partial fulfillment of the rules and regulations for the award of MD degree (branch I) General Medicine.

Place: Madurai

Date: **DR.JEFFEY GEORGE**

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CONTENTS

INTRODUCTION

Idiopathic inflammatory bowel disease (IBD) comprises conditions characterized by a tendency for chronic or relapsing immune activation and inflammation within the gastrointestinal tract. Crohn's disease and ulcerative colitis are the two major forms of idiopathic IBD. They share many clinical and epidemiologic characteristics, suggesting that underlying causation may be similar. Indeed, more than occasionally Crohn's disease cannot be distinguished from ulcerative colitis on clinical grounds, yet the two diseases are distinct syndromes with divergent treatment and prognosis.IBD manifest mainly with intestinal manifestations as well as with extraintestinal manifestations. The various extraintestinal manifestations include musculoskeletal, mucocutaneous, hepatobiliary, hematologic & vascular, ocular, renal& genitourinary manifestations and others. Among these , hepatobiliary manifestation in the form of fatty liver and musculoskeletal manifestation in the form of pauciarthralgia are the most commonly seen.

REVIEW OF LITERATURE

HISTORICAL REVIEW

Although the eponym, “Crohn's disease” has gained general acceptance in recent decades, it was Morgagni who provided a description of intestinal inflammation characteristic of Crohn's disease in 1761[1]. Only after the identification of the tubercle bacillus by Koch in 1882, was it possible to describe persons with ileocecal disease similar to intestinal tuberculosis but lacking the organism. Such reports were provided by Fenwick (1889)[1], Dalziel (1913)[2], Weiner (1914), Moschcowitz and Wilensky (1923 and 1927), and Goldfarb and Suissman (1931)[3]. In 1932, the landmark publication of Crohn and his colleagues Ginzburg and Oppenheimer called attention to “terminal ileitis” as a distinct entity and chronic disease[4].

Dr. Samuel Wilks is credited with being the first to describe Ulcerative Colitis disorder in 1859 when he described this entity as “idiopathic colitis” and recognized it as distinct from the then more common bacillary dysentery[5]. He also reported the pathologic finding of dilated and thinned colon with severe universal inflammation in a patient with this condition[6]. In 1909, Hawkins described the chronic and relapsing nature of the disease course, and the “stealthy hemorrhage” onset of distal disease in which bleeding often occurred in the presence of constipation[7].

DEFINITION

Crohn's disease (CD) is a condition of chronic inflammation potentially involving any location of the alimentary tract from mouth to anus, but with a propensity for the distal small bowel and proximal large bowel. Ulcerative colitis (UC) is a chronic inflammatory disorder of the gastrointestinal tract that affects the large bowel and is a major disorder under the broad group of inflammatory bowel diseases .

GENERAL ASPECTS OF IBD

EPIDEMIOLOGY

CROHN'S DISEASE (CD)

A recent systematic review noted an incidence in North America ranging from 3.1 to 14.6 per 100,000 person-years[8]. It is considerably lower among the non-white population. Female-to-male ratio is between unity and 1.2:1.Crohn's disease is diagnosed most frequently among persons aged 15 to 30 years, the median age of diagnosis to be approximately 30 years[9,10]. Studies have shown a smaller second peak in incidence later in life, generally in the 7th decade[11].

ULCERATIVE COLITIS(UC)

In North America, the incidence rates range from 6.0 to 14.3 cases per 100,000 person-years and the prevalence ranges from 37 to 246 cases per 100,000 persons[12]. In Europe, the incidence rates range from 1.5 to 20.3 cases per 100,000 person-years and the prevalence ranges from 21 to 243 cases per 100,000 persons[12]. These time trends are in contrast with those of Crohn's disease, which has shown an increase in incidence across geographic regions. The prevalence of UC in India has been reported to be substantially lower than that among Europeans[13]. South Asian immigrants in England are more likely to have UC than are European natives[13-15]. UC may present at all ages, although diagnosis before the age of 5 years or after 75 years is uncommon. The peak incidence of UC occurs in the 2nd

and 3rd decades of life. Studies have reported a second, smaller peak in the elderly, between the ages of 60 and 70 years. This second peak is less pronounced than that for Crohn's disease. Most studies have not shown any gender difference in the occurrence of UC and a male-to-female ratio of nearly 1:1 applies to all age groups.

II. AETIOLOGY

A .IMMUNOLOGICAL FACTORS

CROHN'S DISEASE

IBD represents a state of sustained immune response. Many infectious agents have been proposed as the cause of Crohn's disease including Chlamydia, Listeria monocytogenes, cell wall–deficient Pseudomonas species, reovirus, Paramyxovirus (measles virus) and Mycobacterium paratuberculosis. Non-pathogenic commensal enteric flora are sufficient to induce a chronic inflammatory response. The presence of low-level physiologic inflammation within the healthy intestinal mucosa represents a state of preparedness to deal with potentially harmful agents, a more vigorous response would not be appropriate if directed toward the innocuous commensal flora of the gut. Inflammation is kept in check through immune tolerance by subsets of CD4+ helper T cells that are generated in the intestinal mucosa and

secrete the down-regulatory cytokines, transforming growth factor (TGF)-β1 and interleukin (IL)-10. Two specific T cell populations—T regulatory 1 (Tr1) and T helper 3 (Th3) cells—appear to have similar roles in maintaining mucosal tolerance in the intestine[16].When an antigenic challenge occurs, or when tolerance is broken, the immune response may be skewed toward cell-mediated immunity or toward humoral immunity with the production of characteristic cytokine profiles by CD4+ T cell populations. Th1 cells are characterized by their production of a typical cytokine profile of IL-2 and interferon (IFN)-γ. In Crohn's disease, CD4+ T cells have a Th1 cytokine profile, whereas in ulcerative colitis, the cytokine profile is that of a Th2 response, although lacking in IL-4 expression[17].Sustained nature of the inflammation is the result of abnormal barrier function. An intriguing observation in humans is that bone marrow transplantation may cure Crohn's disease[18], whereas small bowel transplantation may not[19]. This observation suggests that immunologic defects, rather than defects intrinsic to the bowel, may be paramount. Poor intestinal barrier function , sustained exaggerated inflammatory reaction from an ineffective immune response, programmed over responsiveness to a persistent stimulus and defective apoptosis[20] accounts for the sustained nature of inflammation in IBD. On activation, macrophages further shape and amplify the immune response by producing IL-2 and the pro-inflammatory cytokines IL-1 and TNF. In

addition to being essential to the formation of granuloma, TNF causes neutrophil activation and along with IFN γ induces the expression of MHC class II on intestinal epithelial cells.

ULCERATIVE COLITIS

The prevailing theory of the pathogenesis of UC emphasizes the role of enteric immune response. The physiologic state of the intestine is one of constant low-grade inflammation in response to environmental stimuli such as bacterial products or endogenous factors. Breaches in this well-regulated mucosal immune system lead to the chronic uncontrolled mucosal inflammation observed in UC. In this regard, immunologic mechanisms in the pathogenesis of UC involve both humoral and cell-mediated responses.

(a)Humoral Immunity

Histologic examination of the inflamed colon indicates a marked increase in the number of plasma cells. This increase is not uniform among cells producing different classes of immunoglobulins. The largest proportional increase occurs in IgG synthesis, which has the highest pathogenic potential among antibody classes. The increase in IgG synthesis in UC is most pronounced in the IgG_1 and IgG_3 subclasses, in contrast to Crohn's disease, in which the increase in IgG_2 synthesis is

more prominent. [21,22] This disparity in the local IgG subclass response likely reflects differences in antigenic stimuli or host immunoregulatory responses between the two groups of IBD patients. The increased IgG synthesis in IBD may represent polyclonal stimulation; however, patients with UC frequently have circulating antibodies to dietary, bacterial, and self-antigens that are mostly of the IgG isotype, usually the IgG_1 subclass. Many of these antibodies are thought to be epiphenomena because the serum antibody titers do not correlate with clinical parameters. Nevertheless, the known cross-reaction between enterobacterial antigens and colonic epithelial epitopes may be an important triggering event, even though, later in the course of the disease, the serum antibody titer to either the bacterial or the colonic antigen may be unimportant. The concept that UC is an autoimmune disease is supported by its increased association with other autoimmune disorders, including thyroid disease, diabetes, and pernicious anaemia[23]. The best characterized intestinal autoantigen is an epithelial antigen of 40-kd size found in normal colonic epithelium.[24] This autoantigen is recognized by IgG eluted from the inflamed colonic mucosa of patients with UC and is a component of the tropomyosin family of cytoskeletal proteins.[25] This autoantibody has the potential to activate complement in vivo, but direct evidence of antibody-induced cytotoxicity has not been observed. The antibody response to this 40-kd protein appears to be unique to UC and is not found in Crohn's disease or

other inflammatory conditions. This autoantigen shares an epitope with antigens found in the skin, bile duct, eyes and joints, [26] [27] sites frequently involved in the extraintestinal manifestations of UC. The precise pathogenic significance of this autoantibody in UC remains unclear at present. An autoantibody that has received significant attention is pANCA.[28] This autoantibody is present in 60% to 85% of patients with UC. [29] [30] It is synthesized within the lamina propria and is of the IgG_1 subclass. The antigen to which the pANCA is directed has not yet been determined with certainty, and a variety of putative antigens have been proposed, including nuclear histone and nonhistone proteins. The most recent evidence suggests that the antigen is a 50-kd nuclear envelope protein that is specific to myeloid cells[31]. The level of pANCA titer does not correlate with disease activity but may decline in patients with long-standing remission or in patients who have had colectomy for at least 10 years. Studies have suggested that pANCA may be associated with a more aggressive disease course[32] and the development of pouchitis following ileal pouch-anal anastomosis (IPAA) in patients with UC.[33]

(b)Cellular Immunity

Immune dysregulation in UC also involves cell-mediated immunity. The mucosal T cells can be divided into two anatomically different groups: lamina propria lymphocytes and intraepithelial lymphocytes (IELs). Immune cells within the lamina propria consist of a mixture of cell

types, including T cells, B cells, macrophages, and dendritic cells. The most common immune cells are IgA-secreting plasma cells. Lamina propria lymphocytes express surface adhesion molecules, α4β7, that provide a homing signal for peripheral immune cells to the mucosal sites.[34] Most investigators have found a similar distribution of T cell subsets ($CD4^+$, $CD8^+$ within the lamina propria in patients with UC compared with that in controls).[35] Lamina propria lymphocytes have been reported to be cytotoxic to autologous colonic epithelial cells, but the exact mechanisms are unknown and the results have not been confirmed.[36] Helper function mainly has involved the effects of T cells on immunoglobulin production by B cells, but the results have been varied and do not provide firm evidence for an underlying immune abnormality in UC. Studies using nonspecific mitogens have found diminished suppressor activity during active disease only, but an antigen-induced suppressor assay has shown that patients with UC in remission exhibited suppressor defects to a range of mycobacterial and enterobacterial antigens.[37] This phenomenon of antigen-induced suppression was predominantly $CD8^+$ cell dependent and correlated with a poor response to skin testing with purified protein derivative; these defects were limited to the peripheral blood and not lamina propria lymphocytes. In patients with UC, the absolute number of IELs is normal or reduced. Most of these cells are $CD8^+$ cells, and the function of IELs has not been well characterized.

It has been suggested that they are cytotoxic and also may be active in suppressing local immune response. In patients with UC, the proportion of IELs using the γδ T cell receptor may increase.[38] However, the function and significance of γδ T cells are unknown. Regardless of their functional status, mucosal T cells within the lamina propria and epithelium as well as peripheral blood T cells display a variety of activation markers, suggesting an activated memory phenotype.[39] Studies have suggested that T cell receptor repertoire is altered in active IBD.[40] Studies have also shown restricted Vβ usage, but there is no distinct pattern when compared with T cells from healthy lamina propria. Although T cell mediated immunity has attracted the most attention in the pathogenesis of UC, nonspecific cellular immunity also is altered. In patients with active disease, there is an overproduction of circulating monocytes as well as mucosal macrophages. [41] The inflamed mucosa of patients with UC also exhibits infiltration of substantial numbers of granulocytes.

Activation of macrophages, lymphocytes and colonic epithelial cells leads to the release of a variety of cytokines and mediators that further amplify the immune and inflammatory response of UC and result in tissue damage. Based on the cytokines they produce, $CD4^+$ T cells have been divided into two major immune phenotypes: T helper 1 (Th1) and T helper 2 (Th2). The Th1 response is characterized by cell-mediated

immunity and is associated with the production of interleukin (IL)-2 and interferon (IFN)-γ. The differentiation of T cells along a Th1 pathway is stimulated by IL-12 generated in response to exposure to infectious agents. The Th2 response is characterized by the production of cytokines IL-4, IL-5 and IL-10, which amplify the humoral immune response. Th1 and Th2 subsets reciprocally down-regulate each other through cytokine production.[42] Both Th1 and Th2 pathways can be regulated by unique regulatory T cells (Th3, T regulatory 1) subsets that produce IL-10 and transforming growth factor-β and down-regulate inflammation.[43] Macrophages in the inflamed colon in patients with active UC synthesize IL-1β, TNF and IL-6, whereas lamina propria T cells probably produce IL-2 and IFN-γ. This immune response can be up-regulated further by presentation of antigen to $CD4^+$ lymphocytes by colonic epithelial cells that express HLA class II antigens.[44] Release of these cytokines also may lead to other abnormalities seen in UC, such as increased epithelial cell permeability and collagen synthesis. Alteration of endothelium by a variety of cytokines may result in local ischemia. Increased expression of endothelial adhesion molecules in response to inflammatory mediators, recruits circulating granulocytes and monocytes to the inflamed tissues, thus further perpetuating the inflammatory response. Elevated cytokine levels within the mucosa also stimulate the release of metalloproteinase from fibroblasts with subsequent matrix degradation. Mucosal

concentrations of many mediators have been shown to be elevated in patients with active UC, including leukotrienes, thromboxane, platelet-activating factor, nitric oxide and reactive oxygen metabolites.[45] These mediators, which are mostly released from active macrophages and neutrophils, contribute to inflammation and mucosal injury, alter epithelial cell permeability, and interfere with iron transport, thereby further contributing to diarrhea. Diarrhea in UC also is caused by complement activation and the release of kinins and other inflammatory mediators from mast cells and eosinophils .

B.GENETIC FACTORS

CROHN'S DISEASE

The relative risk among first-degree relatives is 14 to 15 times higher than that of the general population[46] especially in Eastern European (Ashkenazi) Jews. Studies of monozygotic and dizygotic twins suggest, genetic composition is a more powerful determinant for Crohn's disease than for ulcerative colitis: The concordance rate among monozygotic twins is as high as 67% for Crohn's disease, but only 13% to 20% for ulcerative colitis. Specific IBD genes on chromosome 16 (the IBD1 locus) had been confirmed repeatedly to be linked to Crohn's disease. The IBD1 locus as the NOD2 (nucleotide-binding

oligomerization domain 2) gene, also known as CARD15 (caspase-recruitment domain 15)[47,48] are associated with younger onset of disease, ileal location of disease, and increased likelihood of stricture formation.The OCTN (organic cation transporter) gene, chromosome 5q31 and DLG5, located on chromosome 10q23, may play a role in maintaining normal cellular structure[49,50,51,52]..

ULCERATIVE COLITIS

About 10% to 20% of patients have at least one other affected family member[53].Clinical characteristics of familial disease also have shown that the onset of disease in a child is noted at a much earlier age than in the affected parent, but there is a high degree of concordance between affected siblings for age of onset. Approximately 6% to 16% of monozygotic twin pairs had concordant UC compared with 0% to 5% of dizygotic twin pairs[54,55,56].Linkage studies have suggested that there are susceptibility genes for UC on chromosomes 2, 3, 6, 7, and 12[57,58]. The IBD2 locus on chromosome 12 appears to have the strongest linkage demonstrated in studies involving large numbers of families with UC[59].C3435T polymorphism for the human multidrug resistance 1 (MDR1) gene to susceptibility for UC[60].Association between severe disease and a rare allele of HLA-DR1 (DRB1*0103) has been reported. In

some studies, the HLA-DR3, DQ2 haplotype is associated with extensive colitis, especially among women.

C.ENVIRONMENTAL FACTORS

CROHN'S DISEASE

Breast feeding has been found to be protective for IBD. Occupations associated with outdoor physical labour are relatively under-represented among Crohn's patients, and Crohn's disease has been associated with higher socio-economic status[61].Studies have discerned an increased risk of Crohn's disease among women who use oral contraceptives. Non-steroidal anti-inflammatory drugs (NSAIDs) have been implicated in exacerbations of IBD and as a potential precipitant of new cases. Increased intake of refined sugars and a paucity of fresh fruits and vegetables in the diet have been associated with the development of Crohn's disease. Ulcerative colitis is largely a disease of ex-smokers and non-smokers, whereas Crohn's disease is more prevalent among smokers, and smokers have more surgery for their disease and a greater risk of relapse after resection.

ULCERATIVE COLITIS

No specific infective organism, however, has been isolated consistently from patients with UC. It is possible that products of the commensal flora promote inflammation in the presence of an impaired mucosal barrier or injury to the mucosa[62] and have reduced tolerance

toward their own intestinal flora[63,64]. UC is more common among non-smokers than among current smokers, with the relative risk of UC in non-smokers ranging from 2 to 6[65]. This risk of developing UC with smoking is particularly high for former smokers, especially within the first 2 years of smoking cessation. Smokers also appear to have reduced rates of hospitalization for UC and reduced rates of pouchitis following colectomy[66]. Breast-feeding has been suggested to be protective against the development of UC[67].Studies show a negative association between appendectomy and subsequent development of UC[68,69].

D.PSYCHOGENIC FACTORS

Stress has been shown to increase the severity of colonic inflammation.

III. PATHOLOGY

CROHN'S DIEASE

Focal intestinal inflammation is the hallmark pathologic finding in Crohn's disease. The earliest characteristic lesion of Crohn's disease is the aphthous ulcer. The presence of granulomas is highly characteristic of Crohn's disease. Lately, it show localized foci of architectural distortion unaccompanied by chronic inflammation. Disease becomes chronic and, aphthae may coalesce into larger ulcers with a stellate appearance. The

presence of lymphoid aggregates in both the submucosa and external to the muscularis propria are a reliable sign of Crohn's disease .Large ulcers, sinus tracts, and strictures are late features of Crohn's disease. Fibrosis along with hypertrophy of the muscularis mucosa, may contribute to the development of strictures. Fat wrapping is highly characteristic of Crohn's disease. Crohn's disease has a predilection for the distal small bowel and proximal large bowel. Nearly one half of all patients have disease affecting both ileum and colon. Another one third have disease confined to the small bowel, primarily the terminal ileum and in some cases including the jejunum as well[10].

ULCERATIVE COLITIS

At time of initial presentation, approximately 45% of patients with UC have disease limited to the rectosigmoid, 35% have disease extending beyond the sigmoid but not involving the entire colon, and 20% of patients have pancolitis[70]. The disease typically is most severe distally. In contrast to Crohn's disease, continuous and symmetrical involvement is the hallmark of UC. 75% of patients with left-sided UC may have appendiceal inflammation and patchy inflammation in the cecum[71], resembling the skip pattern characteristic of Crohn's disease. Epithelial regeneration with recurrent attacks results in the formation of pseudopolyps, which is typical of long-standing UC. Another

characteristic appearance of long standing disease is atrophic and featureless colonic mucosa, associated with shortening and narrowing of the colon. Patients with severe disease may develop acute dilatation of the colon. During the healing phase of UC, the inflammatory infiltrate subsides and epithelial regeneration takes place. Classic histologic feature of chronic quiescent UC is crypt architectural distortion or actual dropout of glands. Another characteristic feature of chronic quiescent UC is Paneth cell metaplasia, with the presence of Paneth cells beyond the hepatic flexure, where they typically are absent.

IV.CLINICAL FEATURES

CROHN'S DISEASE

Compared with ulcerative colitis, abdominal pain is a more frequent and persistent complaint. Pain may be intermittent and colicky or sustained and severe and is attributable to inflammation, abscess and obstruction. In contrast with ulcerative colitis, gross rectal bleeding is uncommon and acute hemorrhage is rare[72]. Constitutional symptoms, particularly weight loss and fever, or growth retardation in children, may be prominent and occasionally are the sole presenting features of Crohn's disease. Crohn's disease may be divided roughly into two categories: aggressive fistulizing disease and indolent cicatrizing disease denoted by fibrostenotic stricture[73]; a third subset of patients appear to develop neither

behaviour over long periods of observation. Fistulas are frequent manifestations of the transmural nature of Crohn's disease. Perianal fistulas are common and are estimated to occur in 15% to 35% of patients. Strictures represent long standing inflammation and may occur in any segment of the gastrointestinal tract in which inflammation has been active. Diarrhoea is the most common complaint among patients with Crohn's disease. Increased stool frequency and decreased stool consistency arise through alterations in mucosal function and intestinal motility. Pathophysiology of abdominal pain in due to stretch receptors in the bowel wall which may be stimulated as a food bolus passes through stenotic bowel, leading to abdominal pain and possibly vomiting. Visceral pain may result from inflammation of the serosa. The ganglia of the myenteric plexuses in the intestine in Crohn's disease have been noted to be increased in size and number, possibly indicating neural dysfunction[74].Weight loss and malnutrition are often seen in patients with Crohn's disease and contribute to weakness, irritability, malaise and easy fatigability that are so common. Anorexia, nausea and vomiting also may contribute to weight loss and poor nutrition. Fever associated with active Crohn's disease usually is low grade and may occasionally be the presenting complaint. Anaemia is found in one third of patients with Crohn's disease, primarily as a consequence of iron deficiency from blood loss.

ULCERATIVE COLITIS

The symptom complex tends to differ according to the extent of disease[75]. Patients with proctitis often have local symptoms of tenesmus, urgency, mucus and bleeding, whereas patients with extensive colitis may have more diarrhea, weight loss, fever, clinically significant blood loss and abdominal pain. The median interval between the onset of symptoms and diagnosis of UC is approximately 9 months[76].Rectal bleeding is common in UC. The characteristic of the bleeding is determined by the location of the disease. Patients with proctitis usually complain of passing fresh blood, either separately from the stool or streaked on the surface of a normal or hard stool[77]. Mixture of blood and mucus and may even be incontinent. Diarrhoea is common but not always present. There can be frequent passage of loose or liquid stools and some may have nocturnal diarrhea. Fecal urgency, sensation of incomplete evacuation and fecal incontinence are also common. With left-sided disease, distal transit is rapid, but there is actual slowing of proximal transit, which may help explain the constipation that is commonly seen in patients with distal colitis. Vague lower abdominal discomfort, an ache in the left iliac fosse or intermittent abdominal cramping preceding bowel movements and often persisting transiently after defecation. Severe cramping and abdominal pain and vomiting can occur in association with severe attacks

of the disease. These symptoms, as well as protein loss through inflamed mucosa, hypercatabolism and downregulation of albumin synthesis caused by the inflammation, account for weight loss and hypoalbuminemia. Fever, an additional catabolic factor, usually accompanies severe attacks but is typically of a moderate degree. Patients also may complain of symptoms from anaemia and hypoalbuminemia, including fatigue, dyspnea and peripheral edema. A few patients may present with extra intestinal manifestations such as acute arthropathy, episcleritis and erythema nodosum. Patients with severe attacks also may appear well, but most are ill with tachycardia, fever, orthostasis and weight loss. The abdomen typically is soft with only mild tenderness. Abdominal tenderness may become diffuse and moderate with more severe disease. Bowel sounds may be normal or hyperactive but diminish with progressive disease. In fulminant colitis, the abdomen often becomes distended and firm, with absent bowel sounds and signs of peritoneal inflammation. There may be aphthoid ulceration of the oral mucosa. Clubbing of the fingernails is a frequent manifestation of chronic disease. Peripheral edema may occur secondary to hypoalbuminemia. Minor perianal disease may be present. Signs of extra intestinal manifestations also may be present.

V.ASSESMENT OF SEVERITY OF IBD

CROHN'S DISEASE

Working definition of Crohn's disease activity

MILD TO MODERATE DISEASE

The patient is ambulatory and able to take oral alimentation .

No dehydration, high fever, abdominal tenderness, painful mass, obstruction weight loss less than 10%

MODERATE TO SEVERE DISEASE

Either the patient has failed treatment for mild to moderate disease

More pronounced symptoms including fever, significant weight loss, abdominal pain or tenderness, intermittent nausea and vomiting, or significant anemia

SEVERE FULMINANT DISEASE

Either the patient has symptoms despite outpatient steroid therapy

High fever, persistent vomiting, and evidence of intestinal obstruction, rebound tenderness, cachexia or evidence of an abscess.

ULCERATIVE COLITIS

Truelove and Witts classification

MILD

<4 stools /day, without or with only small amounts of blood

No fever

No tachycardia

Mild anemia

ESR <30mm/hr

MODERATE

Intermediate between mild and severe

SEVERE

>6 stools /day, with blood

Fever>37.5 C

Heart beat>90 beats/min

Anemia with hemoglobin<75% of normal

ESR.30mm/hr

VI. LABORATORY FINDINGS

Anaemia, leukocytosis and thrombocytosis, reflect active disease. Iron deficiency anaemia may be present because of chronic blood loss. Hypoalbuminemia may be seen with both acute and chronic disease. Minor elevations in serum levels of aspartate aminotransferase or alkaline phosphatase also are frequently associated with severe disease, but these changes are transient and return to normal when the disease enters into remission. These abnormalities probably reflect a combination of fatty liver, sepsis, and poor nutrition. Serum inflammatory markers including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may be elevated in active disease. For following clinical changes, CRP is more sensitive than ESR because of the shorter half-life of CRP.

VII.ESTABLISHING THE DIAGNOSIS AND EVALUATION OF DISEASE

CROHN'S DISEASE

No single symptom, sign, or diagnostic test establishes the diagnosis of Crohn's disease. Rather the diagnosis is established through a total assessment of the clinical presentation with confirmatory evidence from radiologic, endoscopic, and in most cases, pathologic findings. Stool studies should include culture, examination for ova and parasites, and testing for Clostridium difficile toxin and should be performed before endoscopy or barium studies. Serology for Entamoeba histolytica should be considered in selected patients. Ultimately, the diagnosis of Crohn's disease is confirmed by findings on barium studies, endoscopy and usually histopathology. Barium studies are especially useful to delineate the late transmural complications of Crohn's disease, but typical findings may be seen early in the disease as well. Early findings include aphthous ulcers, a coarse villus mucosal pattern and thickened folds[78]. Submucosal edema may be evident as thickening or flattening of the valvulae conniventes, whereas transmural edema manifests as widening of the separation between bowel loops. Later findings include a cobblestone appearance resulting from edema and inflammation of relatively spared islands of mucosa separated by intersecting longitudinal and transverse

knifelike clefts of ulceration[78]. Still later, one may discern fistulas, sinus tracts, and fixed strictures.

ULCERATIVE COLITIS

The diagnosis relies on a combination of compatible clinical features, endoscopic appearances and histologic findings. Stool cultures should be obtained to exclude infection with routine bacterial pathogenic organisms; assays for toxins A and B of *C. difficil*e and examinations for ova and parasites also should be performed. Infection with *Escherichia coli* O157:H7 should be considered and requires special stool cultures and special cultures for gonococcus or *Chlamydia* may be necessary in selected cases. In patients presenting with their first attack of UC, sigmoidoscopy with biopsies usually is sufficient to confirm the diagnosis. The hallmark of UC is symmetrical and continuous inflammation that begins in the rectum and extends proximally without interruption for the entire extent of disease. The earliest endoscopic sign of UC is a decrease or loss of the normal vascular pattern, with erythema and edema of the mucosa.. With more severe inflammation, the mucosa may be covered by yellow-brown mucopurulent exudates associated with mucosal ulcerations. Severe UC is associated with mucosa that bleeds spontaneously, and there may be extensive areas of denuded mucosa from severe mucosal ulcerations with diffuse colitis .In long standing UC

pseudopolyps may be present. Barium studies of the colon remain important, however, and may be superior to colonoscopy for evaluation of colonic strictures. The earliest radiologic change of UC seen on barium studies is fine mucosal granularity. With increasing severity, the mucosal line becomes thickened and irregular, and superficial ulcers are well shown en face. Deep ulceration can appear as “collar-stud” or “collar-button” ulcers .

EXTRAINTESTINAL MANIFESTATIONS

CROHN’S DISEASE

It is estimated that one fourth of all patients with Crohn's disease will have an extra intestinal manifestation of IBD[79]. Many of these complications are common to both Crohn's disease and ulcerative colitis and indeed to other nonidiopathic inflammatory conditions of the bowel. In Crohn's disease, the major risk factor for this complication appears to be the number of prior ileal resections[80]. In large series, extra intestinal manifestations are found to occur more frequently in Crohn's disease than in ulcerative colitis and are more common among patients with colonic involvement than in patients with no colonic inflammation. One fourth of those affected will have more than one manifestation[81,82]. Conceptually, these extra intestinal manifestations may be categorized as those

associated with small bowel disease or large bowel disease and those that occur in association with active bowel disease or independent of the state of inflammation. Some complications occur as a direct result of the bowel disease, such as nephrolithiasis resulting from oxalate malabsorption. In the case of inflammatory mucocutaneous, joint, and ocular manifestations, the pathogenesis is an influx of mononuclear cells activated in the gut, but homing aberrantly to the involved extra intestinal organs[83].

MUSCULOSKELETAL MANIFESTATIONS

Among the most common extra intestinal manifestations are disorders of the bones and joints. Clubbing of the fingernails is a common and innocuous finding. More consequential are arthritic manifestations, which are observed more frequently in patients with Crohn's disease than in those with ulcerative colitis. In a study of 976 patients with ulcerative colitis and 483 patients with Crohn's disease, pauciarticular arthropathy (type I, affecting four or fewer joints) occurred in 3.6% of patients with ulcerative colitis and in 6.0% of those with Crohn's disease[84]. In most patients, joint symptoms occurred in the setting of a relapse of bowel symptoms. Polyarticular arthropathy (type II, with five or more joints affected) occurred in 2.5% of patients with ulcerative colitis and 4.0% of those with Crohn's disease[84]. Among patients with Crohn's disease, nearly one half had joint symptoms in association with a relapse in bowel

disease. Distinct HLA genotypes are associated with these two types of peripheral arthropathy—type I: HLA-DRB1*0103, B*35 and B*27; and type II: HLA-B*44[85]. Peripheral arthralgias occur in 16% to 20% of patients with Crohn's disease[82], most strongly in association with colonic disease. Patients tend to have waxing and waning joint pain and stiffness in association with flares of bowel disease. Joints may be involved in an asymmetrical or migratory fashion. Usually, the disease is nondeforming and often is accompanied by skin complications (erythema nodosum) and eye complications (uveitis). Rheumatoid factor typically is negative in these patients. Knee and ankle joints often are affected first, but elbows, wrists, proximal interphalangeal, metacarpophalangeal and metatarsophalangeal joints may be involved subsequently[86]. Patients who have undergone ileocecal resection for their disease tend to have fewer arthritic complications after their surgery[87].

Axial arthropathies are less common than peripheral arthropathies and occur in 3% to 6% of patients with IBD. Spondylitis associated with IBD, like idiopathic ankylosing spondylitis, presents as insidious low back pain and morning stiffness that is improved by exercise. As many as 75% of patients with Crohn's disease and spondylitis may be positive for HLA-B27. Iritis may occur in association with this manifestation. Bilateral symmetrical sacroiliitis without progression to spondylitis is more common than spondylitis and is reported to occur in 4% to 18% of

patients[86]. In one study, radiologic findings of sacroiliitis were detected in 29% of patients with Crohn's disease, although only 3% had symptoms of sacroiliitis[88].

More rare rheumatologic complications include granulomatous vasculitis[89], periostitis, amyloidosis and septic joint. Aseptic necrosis of the hip and other joints may occur with or without the use of glucocorticoids and may be disabling[90]. Osteomyelitis may occur as a result of direct extension by a fistula, usually to the pelvis, or may be a recurrent problem distant from the site of inflammation, presumably through hematogenous spread of bacteria[91].

Metabolic bone disease is common in Crohn's disease; osteopenia or osteoporosis occurs in 30% to 60% of patients. Morbidity as a consequence of increased susceptibility to bone fractures includes debilitating and painful vertebral crush fractures, which may occur even in children with Crohn's disease.

MUCOCUTANEOUS MANIFESTATIONS

The most common skin lesions associated with IBD are pyoderma gangrenosum and erythema nodosum. Neither condition is found solely in IBD, and the finding of one or the other lesion is not specific for either major form of IBD[92]. Pyoderma gangrenosum appears first as a papule, pustule or nodule, most often on the leg or occasionally around a stoma,

and progresses to an ulcer with undermined borders. Pyoderma may, however, occur virtually anywhere on the body. The ulcer typically has a violaceous rim and crater-like holes pitting the base. The phenomenon of pathergy, or the development of large ulcers in response to minor trauma, is characteristic of pyoderma gangrenosum and the skin lesions of Behçet's syndrome[93]. Healing is associated with a classically cribriform, or pocked, scar. In Crohn's disease , pyoderma gangrenosum often occurs without an associated flare of bowel symptoms.

In contrast with pyoderma gangrenosum, erythema nodosum is much more frequently seen in women than in men. The classic appearance is of tender subcutaneous nodules with an erythematous or dusky appearance, most often seen on the pretibial region. There is a strong association with arthropathy. Erythema nodosum often presents during exacerbations of bowel disease and tends to improve with treatment of the underlying bowel disease..

Aphthous ulcers of the mouth are common among patients with Crohn's disease and ulcerative colitis but are also frequently seen among otherwise healthy persons[94]. Angular cheilitis is seen in nearly 8% of patients with Crohn's disease[94].

A rare manifestation is metastatic Crohn's disease, granulomatous inflammation of the skin remote from the gastrointestinal tract , histologically identical to the primary bowel lesion[95]. Described cases

have included lesions behind the ears, in the perineum and on the legs, penis, and vulva. Other rare skin manifestations of Crohn's disease include leukocytoclastic vasculitis[96], Sweet's syndrome (neutrophilic dermatosis)[97], cutaneous polyarteritis nodosa and epidermolysis bullosa acquisita. Some reports have suggested an increased occurrence of psoriasis among patients with Crohn's disease[98].

OCULAR MANIFESTATIONS

Ocular manifestations are estimated to occur in 6% of patients with Crohn's disease[99]. Episcleritis is more common in Crohn's disease than in ulcerative colitis, consists of injection of the sclera and conjunctiva, and does not affect visual acuity. Episodes tend to occur in association with active bowel disease. Scleritis involves deeper layers of the eye and also occurs most often in parallel with active bowel disease but may cause lasting damage if untreated. Uveitis usually presents with headache, deep eye pain, lacrimation, blurred vision and photophobia, as a consequence of iridospasm. Physical examination findings include miosis and ciliary flush. Visual acuity is preserved unless the posterior segment becomes involved. In contrast with the uveitis associated with ankylosing spondylitis, the presentation of uveitis in patients with IBD often is insidious, with bilateral involvement and extension to the posterior segment[100]. Slit-lamp examination demonstrates an inflammatory “flare” in the anterior chamber.. Other ocular complications of Crohn's disease

include a particular corneal injury referred to as keratopathy and night blindness resulting from malabsorption of vitamin A.

HEPATOBILIARY MANIFESTATIONS

Gallstones are found in more than 25% of men and women with Crohn's disease. Asymptomatic and mild elevations of liver biochemical tests often are seen in Crohn's disease, but few of these patients develop clinical evidence of cirrhosis. Primary sclerosing cholangitis(PSC) more often is associated with ulcerative colitis but may occur in 4% of patients with Crohn's disease, usually those with colonic involvement[101]. In patients with Crohn's disease, the inflammatory changes most often are confined to the small biliary radicals and, therefore, the presentation is usually one of abnormal liver biochemical tests, pericholangitis on liver biopsy, and a normal cholangiogram[101]. Other hepatobiliary complications of Crohn's disease include fatty liver and autoimmune hepatitis.

RENAL AND GENITOURINARY MANIFESTATIONS

In addition to the direct complications of perforating Crohn's disease with encroachment on the bladder and other genitourinary structures and inflammatory entrapment of the ureter, uric acid and oxalate stones are common in patients with Crohn's disease. In the setting of fat malabsorption resulting from intestinal resection or extensive small bowel disease, luminal calcium binds free fatty acids, thereby decreasing

the calcium that is available to bind and clear oxalate. Increased oxalate is absorbed as the sodium salt, resulting in hyperoxaluria and calcium oxalate stone formation. Uric acid stones are believed to result from volume depletion and a hypermetabolic state. More rare complications include membranous nephropathy, glomerulonephritis and renal amyloidosis. Penile and vulvar edema also have been reported, but the mechanism for these occurrences is unknown.

COAGULATION AND VASCULAR COMPLICATIONS

A prothrombotic tendency has been noted in both major forms of IBD. Patients may present with venous thromboembolism or, much less commonly, arterial thrombosis. The hypercoagulable state may arise from many possible causes. Contributing factors may include thrombocytosis; increased levels of fibrinogen, fibrinopeptide A, factor V and factor VIII; antithrombin III deficiency; and free protein S deficiency; all are related to active bowel inflammation. Circulating immune complexes, increased levels of plasminogen activator inhibitors, decreased levels of tissue plasminogen activator and spontaneous platelet aggregation may be present independent of bowel inflammation. Increased prevalence of the factor V Leiden mutation has been observed by some[102] but not other investigators[103]. Defective methylenetetrahydrofolate reductase is more prevalent among patients with IBD than it is in the general population[104]. This finding, along with folate and vitamin B12 deficiency, is linked to

hyperhomocysteinemia, which in turn predisposes to thrombosis. In more than one half of patients who experience thrombosis, however, no predisposing factor can be identified[105].

OTHER MANIFESTATIONS

Clinically significant disease of the lungs[106], heart, pancreas and nervous system[107] in association with Crohn's disease is unusual, but reported. Subclinical lung involvement may be much more common than is apparent, perhaps reflecting the commonality of bronchus-associated lymphoid tissue and gut-associated lymphoid tissue[106]. Cardiomyopathy may result from a variety of nutrient deficiencies in patients with marked malabsorption. Pleuropericarditis, myocarditis and endocarditis may occur rarely[108]. Acute pancreatitis[109], granulomatous pancreatitis[110] and pancreatic insufficiency[111] also have been reported.

EXTRAINTESTINAL MANIFESTATIONS

ULCERATIVE COLITIS

These extraintestinal complications are classified by their relations to the activity of the colitis. Manifestations that parallel disease activity usually improve on treatment of the colitis.

DERMATOLOGIC

The most common skin manifestations of UC are complications of drug treatment which include hyper-sensitivity, photosensitivity and urticarial rashes related to sulfasalazine and less commonly to mesalamines. Others are erythema nodosum and pyoderma gangrenosum. Erythema nodosum occurs in 2% to 4% of patients with UC. Its activity typically parallels the activity of the underlying bowel disease. Pyoderma gangrenosum occurs in 1% to 2% of patients. It is usually related to the activity of colitis but may present or persist despite inactive bowel disease. Other less common manifestations associated with UC include Sweet's syndrome or acute febrile neutrophilic dermatosis and pyodermite végétante Hallopeau.

OCULAR

The two most common ocular manifestations associated with UC are episcleritis and uveitis, occurring in 5% to 8% of patients. Episcleritis typically parallels the activity of bowel disease. In contrast, temporal correlation of uveitis with the activity of the colitis is less predictable than with episcleritis.

ORAL

At least 10% of patients with UC, develop oral aphthous ulcers. These lesions usually occur with flares of colitis and resolve on control of the bowel disease. Angular stomatitis and sore tongue are seen in patients

with deficiencies of iron or other micronutrients A rare oral lesion seen in patients with UC is pyostomatitis (pyoderma) vegetans.

MUSCULOSKELETAL

Musculoskeletal abnormalities associated with UC can be either rheumatologic disorders or metabolic bone diseases. Peripheral arthropathy occurs in 5% to 20% of patients with UC. The risk of arthropathy increases with the extent of colonic disease. Peripheral arthropathy can be classified into two distinct types[112].Type 1 is asymmetrical and pauciarticular, affecting fewer than five joints and typically involving the large joints. It parallel the underlying bowel disease activity. Type 2 arthropathy is symmetrical and polyarticular, affecting five or more joints and typically involving the small joints. This type presents with persistent symptoms independent of the colitis activity.

Axial arthropathy occurs less frequently in patients with UC, and includes sacroiliitis and spondylitis. Isolated sacroiliitis occurs in 10% to 15% of patients. It does not usually parallel the activity of the bowel disease. The typical symptom is low back pain. Ankylosing spondylitis occurs in 1% to 2% of patients with UC, and most of these patients are HLA-B27 positive. Patients with UC may develop low bone mineral density due to several factors, including glucocorticoid therapy, low physical activity, and inflammatory cytokines. Osteonecrosis or

avascular or aseptic necrosis of bone or osteochondritis dissecans, is a less common but serious complication in patients with UC.

HEPATOBILIARY

Mild elevations in serum aminotransferase and alkaline phosphatase levels are common in severe attacks of UC. These abnormalities are due be related to a combination of factors, including malnutrition, sepsis and fatty liver. The most important hepatobiliary complication associated with UC is PSC, which occurs in approximately 3% of patients . PSC should be excluded in patients with UC who have persistently abnormal liver tests or evidence of chronic liver disease. PSC is independent of the underlying colitis and it usually follows a progressive course after many years of stable disease.

HEMATOLOGIC

The occurrence of hypercoagulability in UC most commonly manifest as deep venous thrombosis or pulmonary embolism; renal artery thrombosis, cerebrovascular accidents, coronary artery thrombosis and venous thrombosis of mesenteric, portal, and hepatic vessels all have been reported[113,114,115].A variety of coagulation and platelet abnormalities may be present in patients with UC, and include thrombocytosis; increased levels of fibrinogen, coagulation factors V and VIII and

plasminogen activatorinhibitor; and decreased levels of antithrombin III, proteins C and S, factor V Leiden, and tissue plasminogen activator. There may be an increased incidence of factor VLeiden mutation in patients with thromboembolic complications associated with UC. [116,117,118] Another common hematologic complication is anemia. The anemia in patients with UC may be a result of chronic gastrointestinal blood loss, chronic disease, folate deficiency from sulfasalazine therapy or autoimmune hemolysis. Autoimmunehemolytic anemia, usually Coombs positive, may be related to sepsis or glucose-6-phosphate dehydrogenase deficiency in patients on sulfasalazine.

OTHER MANIFESTATIONS

Secondary systemic amyloidosis is a rare but serious complication associated with UC.[119] Pericarditis, Pleuropericarditis and constrictive pericarditis have been reported in patients with UC,[120,121,122,123] although this complication also may be related to mesalamine therapy.[124,125] Patients with UC may also develop abnormalities in pulmonary function, including an increase in functional reserve capacity and a decrease in diffusion capacity.[126] Other pulmonary diseases that have been described in patients with UC include bronchiectasis, bronchiolitis, fibrosing alveolitis, pulmonary fibrosis and pulmonary vasculitis.[127,128,129]

AIMS AND OBJECTIVES

(1) To study the clinical presentation of IBD in our hospital.

(2) To study the extra intestinal manifestations of inflammatory bowel disease

MATERIALS AND METHODS

Setting : Department of Medicine, Govt Rajaji Hospital

Design : Descriptive study

Period of study : Ten months (January2009-October2009)

Ethical approval : Obtained from ethical committee approval headed by Dean, Govt. Rajaji Hospital

Consent : Obtained from all patients

Statistical software : EPI Info 2008

Study population : Patients attending Gastroenterology OPD with bleeding PR who satisfied the inclusion criteria.

Inclusion criteria:

(1) All cases of bleeding PR who satisfied the clinical, colonoscopic and histologic criteria of IBD were included.

(2) All cases of proven UC were also included.

Exclusion criteria:

(1) Positive results for stool culture, ova and parasites and clostridium difficile toxin

(2) Patients with known rheumatological diseases.

(3) Patients with chronic alcoholism.

Thirty nine patients of ulcerative colitis were selected from Gastroenterology OP, Govt. Rajaji hospital, Madurai, presenting with complains of bleeding PR and those who satisfied the clinical, colonoscopic and histologic criteria for IBD .

The duration of illness was upto 10 years, at different stages of Inflammatory bowel disease. Patients with the age group ranging from 15 to 70 years were studied.

The selected patients were evaluated with detailed history regarding duration of disease and symptomatology.

Detailed clinical examination was done. Vitals and temperature of patients were recorded. All systems are examined carefully .

Colonoscopic examination of these patients were done after taking proper consent. Biopsy specimens were taken and sent to Pathology Department of Govt. Rajaji hospital, Madurai for histopathological examination. Extent of the disease was determined by colonoscopy and was classified as distal proctitis, proctosigmoiditis, left-sided colitis (involvement up to splenic flexure) and pancolitis. Severity was assessed using Truelove & Witts criteria. Cases were examined for extraintestinal manifestations. Routine investigations were taken .Liver function tests of these patients were sent. Ultrasound scan of abdomen was done to know the incidence of fatty liver and gallstones at the Radiology Department.

Musculoskeletal manifestations and Dermatological manifestations were noted . Slit lamp examination of eye was done to look for evidence of uveitis.

The information collected regarding all the selected cases were recorded in a Master Chart. Data analysis was done with the help of computer using Epidemiological Information Package (EPI 2008).

Using this software range, frequencies, percentages, means, standard deviations were calculated.

RESULTS AND ANALYSIS OF OBSERVED DATA

A : CHARACTERISTICS OF CASES STUDIED

Table 1 : Age distribution of cases

AGE GROUP	CASES	
	No.	%
Upto 20 year	5	12.8
21-30 years	4	10.3
31 – 40 years	13	33.3
41 – 50 years	5	12.8
> 50 years	12	30.8
Total	39	100
Range	16 – 67 years	
Mean	40.8 years	
S.D.	14.3 years	

The age group most seen in our study was between 31-40 years.

Table 2 : Sex distribution

Sex	CASES	
	No.	%
Male	11	28.2
Female	28	71.8
Total	39	100

Table 3 : **Quantitative parameters**

Parameter	Normal cases		Abnormal cases		***Range***	Mean	S.D.
	No.	%	No.	%			
Hb.%	11	28.2	28	71.8	4.8-13.2	9.96	1.81
TOTAL WBC	26	66.67	13	33.33	6.2-18.7	9.7	3.3

COUNT							
ERYTHROCYTE SEDIMENTATION RATE	11	28.2	28	71.2	20-145	64.1	35.1
PLATELET	28	71.2	11	28.2	1.25-5.17	2.82	0.86
FIBRINOGEN	39	100	-	-	114-450	186	75
AMYLASE	29	74.4	10	25.6	34-185	78.7	44.6
BILIRUBIN	39	100	-	-	0.3-1.1	0.85	0.14
AST & ALT	34	87.2	5	12.8	12-46	23.1	9.2
ALP	39	100	-	-	90-382	158.9	61.7
TOTAL PROTEIN	32	82.1	7	17.9	4.4-7.5	6.45	0.79
ALBUMIN	31	79.5	8	20.5	2.3-4.8	3.59	0.61
GLOBULIN	34	87.2	5	12.8	2.1-3.5	2.86	0.35

In this study 71.8%of patients were anaemic and 71.2%were having elevated ESR. There was no significant elevation of alkaline phosphatase noted.

Table 4 : Colonoscopy findings

	CASES	
Colonoscopy findings	**No.**	**%**
IBD – CD	2	5.1
IBD –UC	37	94.9
Total	39	100

Of the total of 39 patients , 37 had evidence of Ulcerative colitis and 2 were diagnosed with Crohn's disease by biopsy.

Table 5: Biopsy results

Biopsy Findings	**CASES**	
	No.	**%**
Non Caseating granuloma	2	5.1
Active Ulcerative Colitis	37	94.9
Total	39	100

Biopsy of the cases showed non caseating granulomas in Crohn's disease and evidence of active Ulcerative colitis in the rest**.**

Table 6: Truelove & Witts Criteria for disease severity

Truelove & Witts	**CASES**	
	No.	**%**
Mild	1	2.7
Intermediate	6	16.2
Severe	30	81.1
Total	37*	100

***** Two cases are Non Caseating granuloma

Table 7: Extent of disease

Extent of disease	**CASES**	
	No.	**%**
Distal Proctitis (DP)	5	12.8
Distal Procto Sigmoiditis (DPS)	3	7.7
Splenic Flexure (SF)	9	23.1
Total Colitis (TC)	20	51.3
Terminal Ileum & Colon (TIC)	2	5.1
Total	39	100

Out of the 37 cases of UC, 51.3% had evidence of total colitis, followed by involvement upto splenic flexure in 23.1%, distal proctitis in 12.8% and distal proctosigmoiditis in 7.7%.

Table 8: USG Findings

USG Findings	**CASES**			
	Normal		**Abnormal**	
	No	%	No	%
Fatty liver	30	76.9	9	23.1
Gall stones	35	89.7	4	10.3
TOTAL			13	33.3

Fatty liver was the predominant hepatobiliary manifestation in our study in 23.1%.

Table 9: Musculoskeletal manifestations

Musculoskeletal	**CASES**			
	Present		**Absent**	
	No	**%**	**No**	

Low Backache (L)	10	25.	29	74.4
Pauciarticular (P)	10	6	29	74.4
Polyarticular (Py)	3	25.	36	92.3
		6		
TOTAL	23	7.6		
		9		
		58.		
		8		

Pauciarthalgia was the most common musculoskeletal manifestation seen.

Table 10: Mucocutaneous manifestations

Mucocutaneous	**CASES**			
	Present		**Absent**	
	No	**%**	**No**	**%**
Angular Stomatitis (AS)	6	15.3	33	74.62
Pyoderma Gangrenosum (PG)	1	8	38	97.4
Aphthous ulcer (AU)	2	2.56	37	94.87
Erythema Nodosum(EN)	1	5.12	38	97.4
		2.56		
TOTAL SKIN (EN+PG)	2		37	94.8
TOTAL MUCOSAL (AU + AS)	8	5.12	31	79.5
		20.5		

Angular stomatitis was the most seen mucocutaneous manifestation in our study. We had 2.56% each of erythema nodosum and pyoderma gangrenosum in our study.

DISCUSSION

39 patients of IBD from Gastroenterology Department are analysed .Our study has 37 cases of UC and 2 cases of CD.

Of the 37 cases of UC,81% of cases are severe,16% intermediate and 2.6% classified as mild according to the Truelove & Witts criteria. Total colitis is seen in 51.3% of cases followed by left sided colitis in 23.1% , distal proctitis in 12.8% , distal proctosigmoiditis in 7.7%.

Sex ratio of IBD in this study is 1:2.5 . The sex ratio for UC is 1:2.4.According to Harrisons Text Book of Internal Medicine the sex ratio for UC is 1:1 and for CD is 1.1:1.8.

Sleisenger Text Book of Gastroenterology shows a small excess risk of Crohn's disease among women and a female-to-male ratio between unity and 1.2:1. Most studies have not shown any gender difference in the occurrence of UC and a male-to-female ratio of nearly 1:1 applies to all age groups.

The age group with maximum prevalence of disease in our study is 31-40 years**.** The peak incidence of UC occurs in the 2nd and 3rd decades of life and had a second peak incidence above 50 years of age. According to Sleisenger, UC may present at all ages, although diagnosis before the age of 5 years or after 75 years is uncommon .Studies have reported a second, smaller peak in the elderly, between the ages of 60 and 70 years. This second peak is less pronounced than that for Crohn's disease.

Crohn's disease is diagnosed mostly among persons aged 15 to 30 years, although the age of diagnosis may range from early childhood through the entire lifespan. Population-based studies have shown the median age of diagnosis to be approximately 30 years.

Of the 39 patients, 25 patients have anyone of the extraintestinal features, which is 64% in our study.Below is the list of frequency of extraintestinal manifestations in our study compared with published data.

EXTRAINTESTINAL MANIFESTATIONS	**OUR STUDY**	**REFERENCE STUDY**
SEX	**1:2.5**	**1:1.8(**CD**),1:2.4(**UC**)**
AGE GROUP	**31-40 YRS**	**2ND & 3RD** Decade
FATTY LIVER	**23.1%**	**15.4% (**Navneethan et al)
GALL STONES	**10.3%**	**10.5%(**Kurchin A et al**)**
PAUCI ARTHRALGIA	**25.6%**	**16% (**Brinskow et al**)**
POLYARTHRALGIA	**7.69%**	**6.5% (**Brinskow et al**)**
LOW BACK ACHE	**25.6%**	**4-18%(**CD**),10-15%(**UC**)**
ERYTHEMA NODOSUM	**2.6%**	**4.0% (**Fahri et al)
PYODERMA GANGRENOSUM	**2.6%**	**2.3% (**Yuskel et el)
ANGULAR STOMATITIS	**15.38%**	**8%(CD)**
APTHOUS ULCER	**5.12%**	**10%(**UC**)**

FATTY LIVER.

In a study by Navaneethan U[130], Remzi FH et al ,a total of 545 Ileal Pouch Anal Anastomosis patients with underlying IBD which included 346 patients with ulcerative colitis, 25 with indeterminate colitis, and 2 with Crohn's colitis, a total of 17.4% had abnormal LFTs. Of these patients,13.9% had abnormal transaminases. The most common cause of an abnormal LFT was transient elevation in 49.2% patients, followed by fatty liver (fatty change on imaging with body mass index (BMI) >/=25 kg/m(2) in the absence of other causes, including alcohol abuse and drug-induced hepatitis) in 15.4%, drug-induced abnormal LFTs in 7 (10.7%), and chronic hepatitis B or C in 6 (9.2%).

Harrison says Fatty liver is detected in more than 50%of abnormal liver biopsies in IBD.

In our study the incidence is 23.1% and is comparable to the above data.

GALL STONES

Our study, the gall stone incidence is 10.3%.Gall stones are present in both cases of CD and percentage of UC patients with Gallstones is 5.4%.

In a study by Kurchin A, et al[131] ,a retrospective study of 152 ileostomates with inflammatory bowel disease (IBD) revealed that 10.5 per cent had diagnoses of cholelithiasis. The remaining patients, were followed for possible cholelithiasis, with sonographic examination and 23.2 percent were found to have cholelithiasis, usually in an asymptomatic stage. Among women over 50 years old, (63.6 per cent) had gallstones.

Harrison says 10-35%of patients with ileitis or ileal resection have gall stones and that it is more associated with CD.

In a study by Bargiggia S, Maconi G, et al [132],of over three hundred and eleven patients with CD and 200 patients with UC , hepatobiliary abnormalities were found at Ultrasound in 54.2% and 55.9% of CD and UC patients, respectively. Liver enlargement and mild-to-moderate to severe liver steatosis were found in 25.7% and 39.5% of CD patients and in 25.5% and 35.5% of UC patients, respectively. The prevalence of gallstones among CD patients was 11%, higher than that among UC patients (7.5%).

POLYARTRALGIA AND PAUCIARTHRALGIA

In a study by Orchard TR, et al[112], 976 patients with ulcerative colitis and 483 patients with Crohn's disease were reviewed. Type 1 arthralgia occurred in 3.6% of patients with UC and in 6.0% of those with CD.

Type 2 occurred in 2.5% of patients with UC and 4.0% of those with CD .

Brynskov J, Binder V.et al [133]reported mild arthritis/arthralgias as the most frequent extraintestinal manifestation in inflammatory bowel disease (IBD) and to occur in 10-35% of patients.

D'Incà R, Podswiadek M, et al[134] in a cohort of 651 patients reported that arthropathy was axial in 52%, oligoarticular in 16% and polyarticular in 23%.

In our study the percentage of pauciarthralgia and polyarthralgia are 25.6% and 7.69 % respectively.

LOW BACK ACHE

Axial arthropathy manifesting as sacroiliitis or low backache is reported in 25.6% in our study.

Sleisenger says isolated sacroiliitis occurs in 10-15% of cases of UC and bilateral symmetrical sacroiliitis without progression to spondylitis occurs in 4-18% of CD

ERYTHEMA NODOSUM

Our study has one case of erythema nodosum. Prevalence of EN in our study is 2.6% . EN was diagnosed in a female patient with Crohn's disease in our study.

In a study by Farhi D,et al[135]among 2402 patients with Crohn disease (63.3%) and ulcerative colitis (31.0%), 5.8% had at least 1 skin manifestation. The most frequent dermatologic symptom was erythema nodosum **(**4.0%). Erythema nodosum was significantly and independently associated with a diagnosis of Crohn's disease and female sex .

Yüksel I,et al[136] , out of 352 patients studied, 9.3% had at least 1 major cutaneous manifestation. The prevalence of EN in IBD was 7.4%. Erythema nodosum was more common in Crohn's disease than in ulcerative colitis.

In a study by Moravvej H et al[137], the prevalence of cutaneous manifestations in ulcerative colitis was 4.07%, and more frequent in females (52%) than in males (48%) . Also, Erythema nodosum was diagnosed only in female patients with Crohn's disease in that study .

PYODERMA GANGRENOSUM

Yüksel I,et al[136], studied 352 patients and 34 patients (9.3%), who presented with at least 1 major cutaneous manifestation. The prevalence of Pyoderma gangrenosum in their study was 2.3%.In a study by Moravvej H,et al[137], the prevalence of cutaneous manifestations was 5.9%. These manifestations were higher in Crohn's disease (7.29%) than in ulcerative colitis (4.07%), more frequent in females (52%) than in males (48%) and pyoderma gangrenosum was seen more often in ulcerative colitis.

In our study the frequency of PG is 2.56%and is associated with UC. The percentage of UC patients with PG is 2.7%.

APHTHOUS ULCER

Aphthous ulcer is present in 5.12% of patients in our study. Sleisenger says aphthous ulcers of the mouth are common among patients with Crohn's disease and ulcerative colitis but are also frequently seen among otherwise healthy persons. At least 10% of patients with UC develop oral aphthous ulcers. These lesions usually occur with flares of colitis and resolve on control of the bowel disease.

ANGULAR STOMATITIS

It is present in 15.38% of patients examined in our study.Out of the 2 cases of CD, angular stomatitis is found in one case. Angular stomatitis is seen in nearly 8% of patients with Crohn's disease according to Sleisenger .

In a study by Moravvej H et al[138], the prevalence of cutaneous manifestations in ulcerative colitis was 4.07% , and was more frequent in females (52%) than in males (48%). Aphthous stomatitis was observed more frequently in Crohn's disease.

CONCLUSION

1. Ulcerative colitis is more prevalent than Crohn's Disease in our study.
2. Sex ratio of Inflammatory Bowel Disease, M:F = 1:2.5
3. The peak age group affected by IBD is 31-40yrs.
4. Total colitis is the predominant colonoscopic finding in our study.
5. The majority of Ulcerative colitis cases are having severe disease (81.1%) based on Truelove & Witts criteria.
6. Extraintestinal manifestations of IBD in our study is 64 %. (25patients)
7. The most common extraintestinal manifestations are Pauciarthralgia (25.6%) & Fatty liver (23.1%)
8. No cases of Primary Sclerosing Cholangitis and eye manifestations like uveitis are found in our study
9. The extraintestinal manifestations in our study are comparable to published literature worldwide.

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SUMMARY

The study “EXTRA INTESTINAL MANIFESTATIONS OF INFLAMMATORY BOWEL DISEASE ” is a cross sectional study conducted on patients visiting the outpatient Department of Gastroenterology ,Government Rajaji Hospital , Madurai.

Our aim was to study the clinical presentation of IBD in our hospital and the extraintestinal manifestations of the disease. All cases of bleeding PR who satisfied the clinical, colonoscopic and histologic criteria of IBD were included as well as cases of proven IBD.

Thirty nine patients with inflammatory bowel disease were included in the study. Colonoscopic examination of these patients were done after taking proper consent. Extent of the disease was determined by colonoscopy. Biopsy specimens were taken and sent for histopathological examination. Severity of disease was assessed by Truelove & Witts criteria. Selected patients underwent clinical and laboratory evaluation to detect the extraintestinal manifestations.

The information collected regarding all the selected cases were recorded in a Master Chart and data analysis done with the help of Epidemiological Information Package (EPI 2008).

Analysis of data shows that Ulcerative colitis is more prevalent than Crohn's disease in our study and that IBD manifestations are seen predominantly in females. The age group with maximum prevalence of disease in our study is 31-40 years .Total colitis is the most common colonoscopic finding seen. Of the 39 patients, 25 patients have at least one extraintestinal feature, which accounts to 64% in our study. Pauciarticular arthralgias and Fatty liver are the most frequently found extraintestinal manifestations.

Our study had only 39 patients and a larger patient population could throw more light on the extraintestinal manifestations.

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GLOSSARY

IBD	-INFLAMMATORY BOWEL DISEASE
CD	-CROHNS DISEASE
UC	-ULCERATIVE COLITIS
FL	-FATTY LIVER
GS	-GALL STONES
EN	-ERYTHEMA NODOSUM
PG	-PYODERMA GANGRENOSUM
L	-LOW BACK ACHE
AU	-APHTHOUS ULCER
AS	-ANGULAR STOMATITIS
P	-PAUCIARTICULAR ARTHROPATHY
Py	-POLYARTICULAR ARTHROPATHY
N	-NORMAL
SF	-SPLENIC FLEXURE
DPS	-DISTAL PROCRO SIGMOIDITIS
DP	-DISTAL PROCTITIS
TC	-TOTAL COLITIS
TIC	-TERMINAL ILEUM & COLON
S	-SEVERE DISEASE , M - MILD DISEASE
I	-INTERMEDIATE DISEASE

PROFILE OF IBD AND EXTRAINTESTINAL MANIFESTATION

NAME **AGE** **SEX**
ADDRESS **IP No**
OCCUPATION

SYMPTOMS **ULCERATIVE COLITIS** **CROHNS**
WITH DURATION Rectal bleeding Diarrhoea
Diarrhoea Abd. Pain
Abd. pain weight loss/malnutrition
Anorexia/nausea Anorexia/nausea
Fever Fever
Anaemia

PAST H/O
h/o HT/ DM /PTB /IHD /Stroke
h/o Sx (ileocaecal)
h/o malignancy
h/o appendectomy

PERSONEL H/O Smoking – duration
Alcohol / pan chewing
STD

FAMILY H/O H/o malignancy / similar illness

DRUG H/O Previous treatment / steroids

O/E
PR BP RR Ht Wt
Pallor
Clubbing
Cyanosis
Pedal edema
Gen. Lymphadenopathy

1 P/A
Penile /vulvar d/s
Anal fissure / fistula /perirectal abcess
Per rectal examination

2 CVS
Cardiomyopathy
Myo / endocarditis
Pleura pericarditis

3 Resp.
4 CNS
5 Ocular

Episceritis
Scleritis
Uveitis
Keratopathy
Nt blindness

Musculoskeletal : clubbing
Arthritis pauci / poly
Low backache
Axial arthropathy
Septic joint
Osteopenia /osteoporosis

Muco cutaneous

Pyoderma gangrenosom
Erythema nodosum
Apthous ulcer
Angular chelitis
Cutaneous PAN
Leucocytoclastic vasculitis
Psoriasis
Epidermolysis bullosa congenita

INVESTIGATIONS

Hb TC DC ESR
CRP
Hct Plt Fibrinogen
LFT **EYE slit lamp examination** Rt
Lt

Ant chamber
Amylase Post chamber
USG Fatty liver
Gall stones

OGD
Colonoscopy / sigmoidoscopy
Biopsy

CDAI	**UCDAI**
Liquid/very soft stools	stool freq
Abd. Pain	rectal bleeding
Gen well being	Mucosal appearance
EI disease	physician global assessment
Abd mass	

HCT
Body weight

Disease extent

Ulcerative colitis	**Crohn's**
Rectum only	Colitis only
Distal to splenic flexure	Ileocolonic
Subtotal colitis	Terminal ileum +caecum
Total colitis	Prox small bowel only
	Ext. Small and large bowel

ETHICAL COMMITTEE APPROVAL

TOPIC : clinical ,extraintestinal and colonoscopic manifestation in biopsy proven cases of Inflammatory bowel disease
Done by : Dr Jeffey George
Approval order No : K . Dis No. 4735/E4/1/2008
Government Rajaji Hospital , Madurai.
Dated 28.11.2008